FROM THE ANALYST'S COUCH

Trends in the market for antihypertensive drugs

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Hypertension, or prolonged and persistent elevation in blood pressure, is one of the most important risk factors for mortality and morbidity due to cardiovascular disease. An estimated one billion people are affected by hypertension worldwide and the condition accounts for more than half of the 17 million deaths caused by cardiovascular disease each year. Approximately 5% of hypertensive patients have an underlying cause (for example, kidney disease) for their disease, but the vast majority are diagnosed with 'essential hypertension' with unknown aetiology. Pulmonary arterial hypertension (PAH) is a subtype of hypertensive disease in the arteries connecting the right side of the heart to the lungs. It can be associated with other conditions, including connective tissue disease, and it has been the focus of efforts to develop PAH-specific interventions.

Current therapies

US guidelines encourage physicians to put recently diagnosed patients with hypertension on the DASH (Dietary Approaches to Stop Hypertension) diet, which can lower blood pressure within 2–3 weeks. When patients do not achieve adequate reductions in blood pressure, pharmacological intervention is required. First-line agents include various drugs that have been generic for many years, such as the vasodilating agents hydralazine and minoxidil, the thiazide diuretics hydrochlorothiazide and chlorthalidone, the beta-blockers atenolol and metoprolol, and angiotensin-converting enzyme inhibitors (ACEIs) such as captopril and enalapril. More recently approved drugs, such as the calcium channel blockers (CCBs) amlodipine and nifedipine, and angiotensin II receptor blockers (ARBs) such as valsartan, telmisartan, irbesartan and olmesartan, are also now generic. The most recent approval of a drug in a new class was the direct renin inhibitor, aliskiren (Tekturna; Novartis), in 2007.

Many of these drugs are limited by issues including side effects, poor bioavailability and lack of applicability across a range of hypertensive patient groups. Despite the global burden of hypertension, the number of novel drugs reaching the market in the past decade has been disappointingly low and most patients who are treated with existing monotherapies fail to achieve target blood pressure.

Reflecting the issues with existing monotherapies and the challenges of developing antihypertensive drugs with new mechanisms of action, many companies have focused on developing fixed-dose combinations (FDCs) of two or more agents, and dozens of such FDCs have been approved in the past 15 years. There are several advantages to formulating antihypertensive drugs as FDCs. Data from clinical trials show that the ARB valsartan and the CCB amlodipine have a synergistic effect in reducing the peripheral oedema associated with the use of CCBs alone when formulated as an FDC. The use of FDCs can also reduce the side effects of the individual monotherapies, as the dosage of each active ingredient in the FDC pill is lower than the dosage of the respective drug when prescribed as monotherapy. Moreover, the prescription of a single FDC aids compliance when compared with the prescription of multiple monotherapies. This can lead to indirect cost savings owing to the prevention of hospitalization and direct cost savings in the form of lower prescription costs. From a commercial perspective, this approach has also provided companies with an opportunity to introduce new branded antihypertensive products and reduce the impact of generic entries on their franchises.

While FDCs have dominated recent drug development efforts for hypertension in general, there has been more innovation with drugs for PAH. The pioneering endothelin ▶

Table 1 | **Selected late-stage antihypertensive products**

Drug	Developers	MOA	Status
Candesartan cilexetil/nifedipine	Bayer	ARB/CCB	Phase III
Fimasartan/amlodipine	Boryung Pharmaceutical	ARB/CCB	Phase III
Fimasartan/hydrochlorothiazide	Boryung Pharmaceutical/ Stendhal Mexico	ARB/diuretic	Phase III
Telmisartan/chlorthalidone	HanAll Biopharma	ARB/diuretic	Phase III
Telmisartan/amlodipine/ hydrochlorothiazide	Boehringer Ingelheim	ARB/CCB/ diuretic	Approved (Japan)
Telmisartan/amlodipine/ chlorthalidone	Yuhan	ARB/CCB/ diuretic	Phase III
Azilsartan/amlodipine/ hydrochlorothiazide	Takeda	ARB/CCB/ diuretic	Phase III
Losartan/atorvastatin	Yuhan/HanAll Biopharma	ARB/statin	Pre-registration
Valsartan/pitavastatin	JW Pharmaceutical	ARB/statin	Phase III
Candesartan cilexetil/rosuvastatin	Alvogen	ARB/statin	Phase III
Valsartan/amlodipine/rosuvastatin	CJ Healthcare	ARB/CCB/statin	Phase III
Amlodipine/celecoxib	Kitov Pharmaceuticals	CCB/NSAID	Phase III
CS 3150	Daiichi Sankyo	MRB	Phase III
HCP 1401 and HCP1305	Hanmi Pharmaceutical	Other FDCs	Phase III
Bardoxolone methyl	Reata Pharmaceuticals/ Kyowa Hakko Kirin	AIM agent	Phase III
Esuberaprost	Lung Biotechnology	Prostaglandin receptor agonist	Phase III
Nitric oxide inhalation (INOpulse)	Bellerophon Therapeutics	sGC stimulant	Phase III

AIM, antioxidant inflammation modulator; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; FDC, fixed-dose combination; MOA, mode of action; MRB, mineralocorticoid receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; sGC, soluble guanylate cyclase.

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receptor antagonist bosentan (Tracleer; Actelion) was approved in 2001, and has been followed by the second-generation drugs ambrisentan (Letairis; Gilead) in 2007 and macitentan (Opsumit; Gilead) in 2013. Two phosphodiesterase 5 inhibitors first approved for erectile dysfunction, sildenafil (Revatio; Pfizer) and tadalafil (Adcirca; United Therapeutics/Eli Lilly), were approved for PAH in 2005 and 2009, respectively. The soluble guanlyate cyclase stimulator riociguat (Adempas; Bayer) was approved for PAH and also chronic thromboembolic pulmonary hypertension in 2014, and the prostacyclin receptor agonist selexipag (Uptravi; Actelion/Nippon Shinyaku) was approved for PAH in 2015.

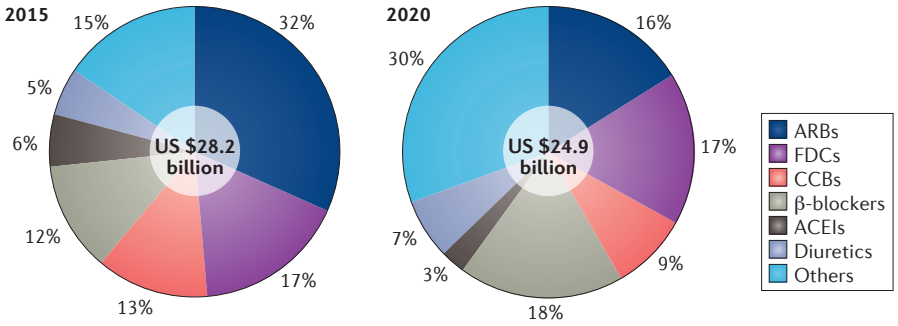

Figure 1 | **Global sales of antihypertensive drugs.** In 2015, angiotensin II receptor blockers (ARBs) comprising several leading brands (such as Benicar (olmesartan medoxomil; Daiichi Sankyo), Diovan (valsartan; Novartis) and Micardis (telmisartan; Boehringer Ingelheim)) led the market, followed by fixed-dose combinations (FDCs). The 'others' category includes endothelin receptor antagonists such as Tracleer, Opsumit (bosentan and macitentan, both Actelion) and Letairis (ambrisentan; Gilead). All drug classes, except FDCs, represent sales of monotherapies. ACEIs, angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers.

Late-stage pipeline

Most late-stage antihypertensive drugs in the pipeline (TABLE 1) consist of dual or triple combinations involving an ARB. Phase III trials are under way for candesartan cilexetil/nifedipine (Bayer) and fimasartan/amlodipine (Boryung Pharmaceutical), both of which are FDCs of an ARB and a CCB. Recent results from the DISTINCT trial show that candesartan cilexetil/nifedipine is more effective than nifedipine monotherapy and that it has greater efficacy in lowering blood pressue across various ethnic groups. Another FDC in phase III development contains a combination of fimasartan and hydrochlorothiazide (Boryung/Stendhal Mexico). The presence of fimasartan — an ARB with selectivity for angiotensin II type 1 (AT_1) receptor subtype — in this FDC offsets the increase in plasma renin activity due to the hydrochlorithiazide. This combination achieved better blood pressure control than fimasartan alone, with comparable safety and tolerance. A combination of chlorthalidone (a thiazide-like diuretic) with the ARB antagonist telmisartan (HanAll Biopharma) is also in phase III trials. Three ARB/CCB/diuretic triple combination products are in the late-stage pipeline; a telmisartan/amlodipine/hydrochlorothiazide (Micatrio; Boehringer Ingelheim) combination has received approval in Japan while a telmisartan/amlodipine/chlorthalidone (Yuhan) combination and azilsartan/amlodipine/hydrochlorothiazide (Takeda) FDCs are in phase III trials. Amlodipine is the preferred CCB in all dual and triple combination products, reflecting its minimal risk profile for cardiovascular events and longer duration of action compared with nifedipine.

Several ARB/statin FDCs, which could tackle the related conditions of hyperlipidaemia and hypertension, are also in the later stages of the pipeline. The most advanced is HanAll's losartan/atorvastatin FDC pill, which is at the pre-registration stage in South Korea and in phase II trials in the United States. The tablet formulation of losartan/atorvastatin provides staggered release of both drugs, making side effects less likely and increasing compliance. Two other dual combinations, valsartan/pitavastatin (JW Pharmaceuticals) and candesartan cilexetil/rosuvastatin (Alvogen), are also in phase III trials. Meanwhile, CJ Healthcare has two ARB/CCB/statin triple combinations in development, differing only in the statin used. Valsartan/amlodipine/rosuvastatin is in phase III trials while valsartan/amlodipine/atorvastatin is in phase I trials.

Kitov Pharmaceuticals has recently completed phase III trials with a capsule formulation of amlodipine/celecoxib for hypertension and pain in osteoarthritis patients. The FDC represents a rare combination of a CCB with a nonsteroidal anti-inflammatory drug. Celecoxib, a selective oral cyclooxygenase-2 (COX2) inhibitor, is intended to deliver pain relief in osteoarthritis patients while amlodipine is used as part of the FDC formulation to reduce blood pressure, as NSAIDs are known to raise blood pressure as a side effect. A new phase III trial is planned after pharmacokinetic data suggested that this FDC improves renal function.

Other emerging antihypertensives include esaxerenone (Daiichi Sankyo) and two unspecified formulations (HCP 1401 and HCP 1305; Hanmi Pharmaceutical). Esaxerenone is a selective nonsteroidal mineralocorticoid receptor blocker that has the potential to treat several conditions, including hypertension, heart failure and diabetic nephropathy. Daiichi Sankyo initiated phase III trials in Japan comparing esaxerenone with the antimineralocorticoid eplerenone (Inspra; Pfizer) in September 2016.

Late-stage PAH-specific products include bardoxolone methyl (Reata Pharmaceuticals), esuberaprost (Lung Biotechnology) and Bellerophon Therapeutics' INOpulse inhaled delivery of nitric oxide.

Market indicators

The global market for antihypertensive drugs generated revenues worth US$28.2 billion in 2015 (FIG. 1), but for the period 2013–2015, the market contracted, with an associated compound annual growth rate (CAGR) of –11.0% from a high of $35.6 billion in 2013. The market is projected to contract further, reaching $24.9 billion by 2020 (CAGR –2.5%, 2015–2020), in the face of increasing generic competition and continued cost-containment pressures on health-care providers.

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The authors would like to thank Dr Sharmarke Mohamed, Khalifa University, Abu Dhabi, for his critical comments and feedback on the article.

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doi:10.1038/nrd.2016.262
Published online 10 Mar 2017
The authors declare no competing financial interests.